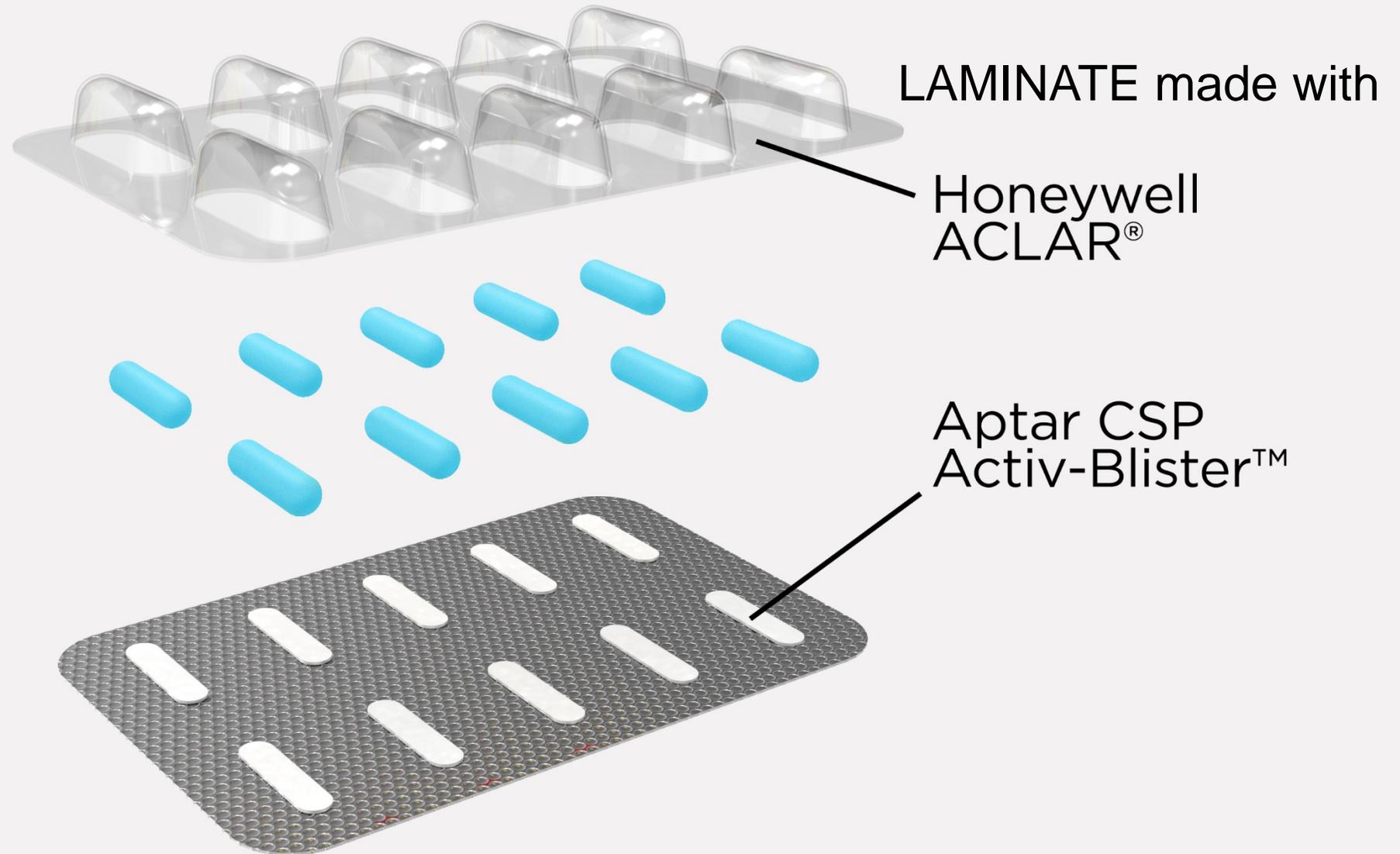


Active Packaging Reimagined: Novel Technologies to Derisk Drug Product Stability



Presenters



Kori Anderson

General Manager, Life Science Packaging
Honeywell International



François Bidet

VP Business Development, EMEA
Aptar CSP Technologies



Dr. Thomas Dries

Global Market Development Manager
Honeywell International



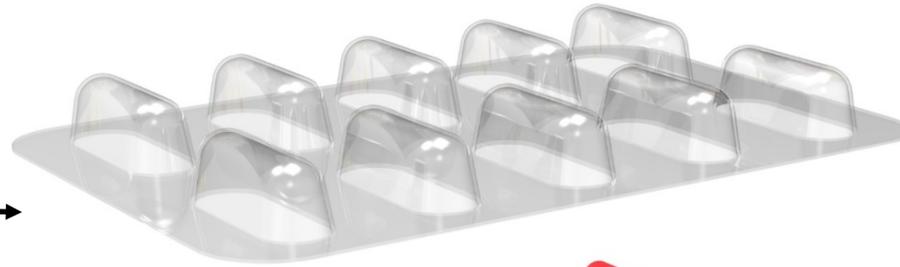
Jim Hollinger

Activ-Film™ Business Unit Manager
Aptar CSP Technologies

Mitigate the Moisture Problem within the Pharma Industry

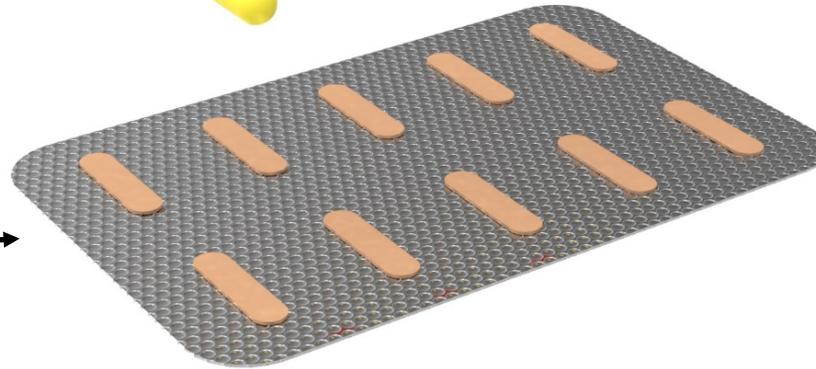
Oral Solid Doses | Tablets and Capsules

**Thermoformed Aclar® Laminate
Passive Moisture Barrier Film**



Honeywell

**Activ-Film™ affixed to foil,
Active Moisture Scavenging film**



Aptar
CSP Technologies

Honeywell Overview

NYSE: **HON*** | ~970 sites | ~110,000 employees | **Charlotte, N.C.** headquarters | **Fortune 100**

Aerospace



Our products are used on virtually every commercial and defense aircraft platform worldwide and include aircraft propulsion, cockpit systems, satellite communications, and auxiliary power systems.

Building Technologies



Our products, software, and technologies are in more than 10 million buildings worldwide, helping customers ensure their facilities are safe, energy efficient, sustainable, and productive.

Performance Materials and Technologies



We develop advanced materials, process technologies, automation solutions, and industrial software that are revolutionizing industries around the world.

Safety and Productivity Solutions



We improve enterprise performance and worker safety and productivity with our scanning and mobile computers, software, warehouse automation solutions, and personal protective equipment.

 *Honeywell Rejoins the Dow Jones Industrial Average

Aligned to Key Global Macro Trends

Life Sciences | Honeywell Solutions

Technology + KnowHow + VOC across the Life Sciences Value Chain



AM

Research Chemicals
(Burdick & Jackson™, Fluka™,
Riedel-de Haën™)

Aclar® Film Blister
Aclar Edge™ Bottles and Vials



Digital Authentication

Spectra® Medical
Grade Fiber

HPS

HPS Experion® Batch Plant &
Personnel Safety Integrated Data

Cyber Security Solutions

Next Opportunities: QMS, MES; GMP compliant data
integration, visualization and predictive analytics

UOP

Callidus Thermal Oxidizers

Molecular Sieve API

SPS

Movilizer Track & Trace
RFID Labels

Connected Freight

Connected Medical Solutions

Industries:

Pharmaceutical | Healthcare | Medical Devices | Chemicals | Cosmetics/Cosmeceuticals | Research & Development | Traditional Medicine
Diagnostics | Nutraceuticals | Biotechnology | Generics | Gene & Cell Therapy | GxP | 21CFR Part 11 | EH&S | Food & Beverage | Vaccines | OTC

One Company: Solutions Across the Life Sciences Value Chain

Aptar CSP Technologies Overview

 Prescription Consumer Health Care	 Beauty Personal Care	 Food Beverage	 Material Science Active Packaging
Injectables 	Gift & Promotion 		
			

- **Leader in the global dispensing systems industry** with over half a century of experience operating in consumer packaging
- **Adding value** to the world's best known products
- **Worldwide presence** with operations in 19 countries
- Publicly traded on **NYSE (ATR)**
- **Strong** balance sheet

About Aptar CSP Technologies

- Headquarters Auburn, Alabama, USA, with global footprint
- Material science specialist delivering innovative, highly-engineered, active packaging solutions
- + 1 billion components manufactured annually, 4 manufacturing locations worldwide
- + 500 worldwide patents
- Active in pharmaceutical, diagnostics, probiotics and food safety



Auburn, AL USA



Guangzhou, China



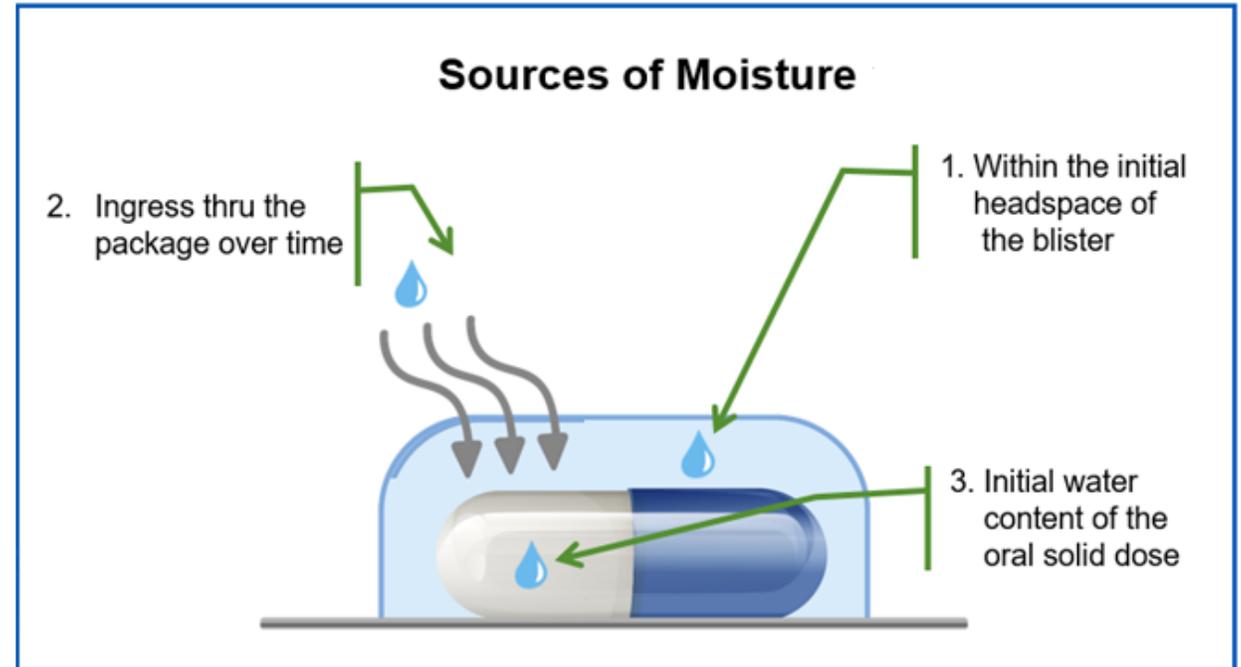
Atlanta, GA USA



Niederbronn-les-Bains, France

Sources of Moisture and Impact on Stability of Oral Solids

- **Three main sources of moisture in OSDs:**
 - Permeation through the primary packaging over time
 - Initial water content (RH) from granulation
 - Initial moisture in the headspace
- **Main impact of moisture on OSDs**
 - Accelerated degradation of API
 - Changes in physicochemical properties
 - Reduced shelf-life



Main Reasons for Moisture Sensitivity of Oral Solids

Poor solubility of majority of drugs

- ~ 40% of marketed drug and ~90% of drugs in clinical trials (1)
 - Amorphous forms or crystal polymorph (2)
 - Particles size reduction to increase dissolution rate
 - Surfactants for wettability

Moisture-induced physical stability issues

Formulation Complexity

Growing # of LCM (Life Cycle Management) projects

- Fast dissolve incl. oral dispersible tablets
- Extended Release
- Residual moisture from wet granulation & drying

Formulation vulnerable to moisture (4)

Chemical Stability

- ~ 25% marketed drug products are sensitive to moisture (3)
 - Moisture-induced gain in chemical degradation rate
 - Hydrate-formation
 - Hydrolysis (4)

Moisture dominant factor for chem. degradation

Globalization

Stability testing requirements for climatic zones IVA & IVB

CZ	Climate	Criteria (annual means)	Test Conditions
IVA	Hot & humid	T > 22°C / p > 15 – 27 hPa	30°C / 65% rH
IVB	Hot & very humid	T > 22 °C / p > 27 hPa	30°C / 75% rH

High stress on DPs in hot & (very) humid CZs

Proper protection against moisture impact on formulation – key to success

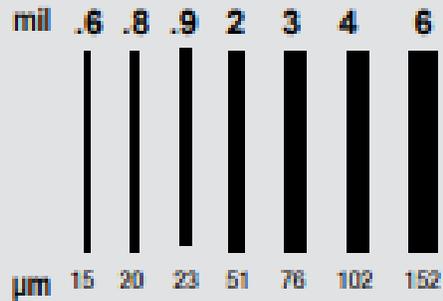
The Aclar Portfolio

POSITIONING: ACLAR FLAGSHIP/ACLAR ACCEL



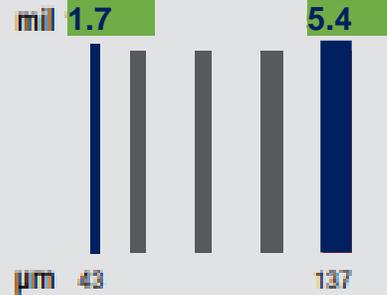
Honeywell Aclar®

- Premium flagship offering
- Custom dimensions
- Suite of design services



Honeywell Aclar Accel

- Faster delivery
- Standard dimensions
- More cost-effective



Aclar Accel 1700 vs. HB PVdC

- Non-yellowing film for highest clarity
- Cost effective transparent barrier film



Aclar Accel 5400 vs. Alu/Alu

- Improved total cost effectiveness compared to Cold Form Foil
- Designed for opaque laminates

Aclar[®] Benefits versus Alu/Alu | Blister Packaging

User Experience

- Confidence – less medication errors from see-through / clarity
- Tablet extraction – control of push-through forces
- Portability – up to 62% smaller footprint vs Alu/Alu

Example 1



Example 2



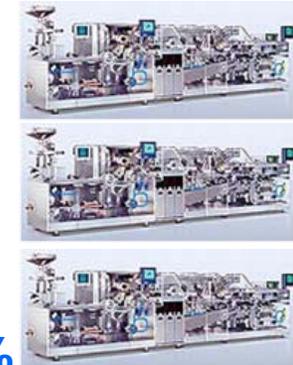
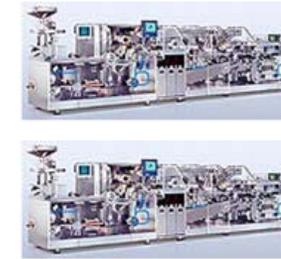
Footprint reduction

62%

59%

Productivity

- Up to 50% capacity gain in packaging operations
- Up to 66% gain in pallet efficiency
- Up to 66% gain in warehouse space



Manufacturing time reduction 33%

Sustainability

- Up to 66% reduction in shipping volume
- Up to 20% reduction in packaging weight
- Up to 25% less energy from manufacturing, warehousing and outbound transportation

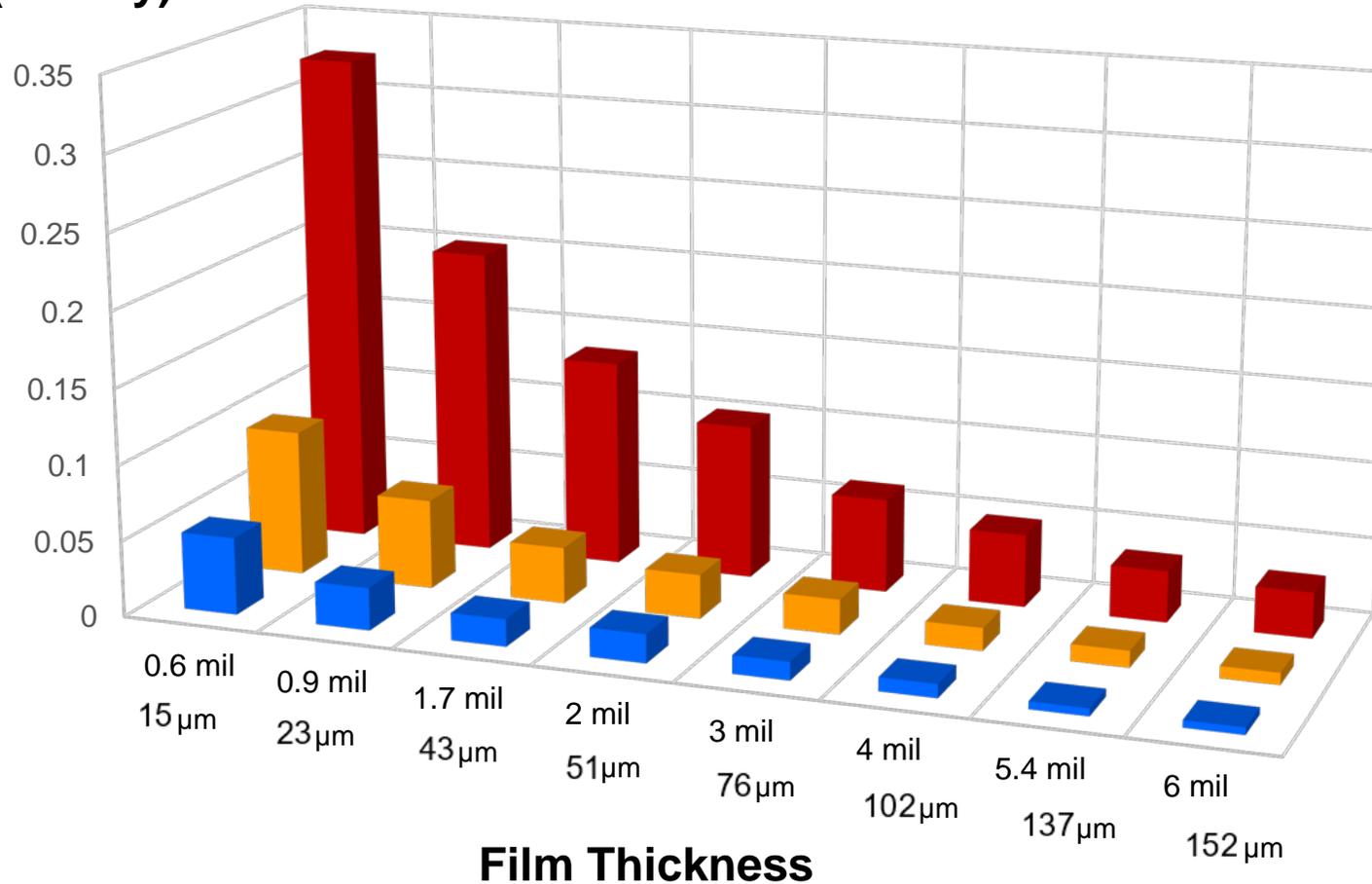


Outbound shipping reduction 66%

Significant Benefits versus Alu/Alu

Aclar MVTR (Flat-Film) @ Accelerated & ICH Testing Conditions

g/(m²*day)



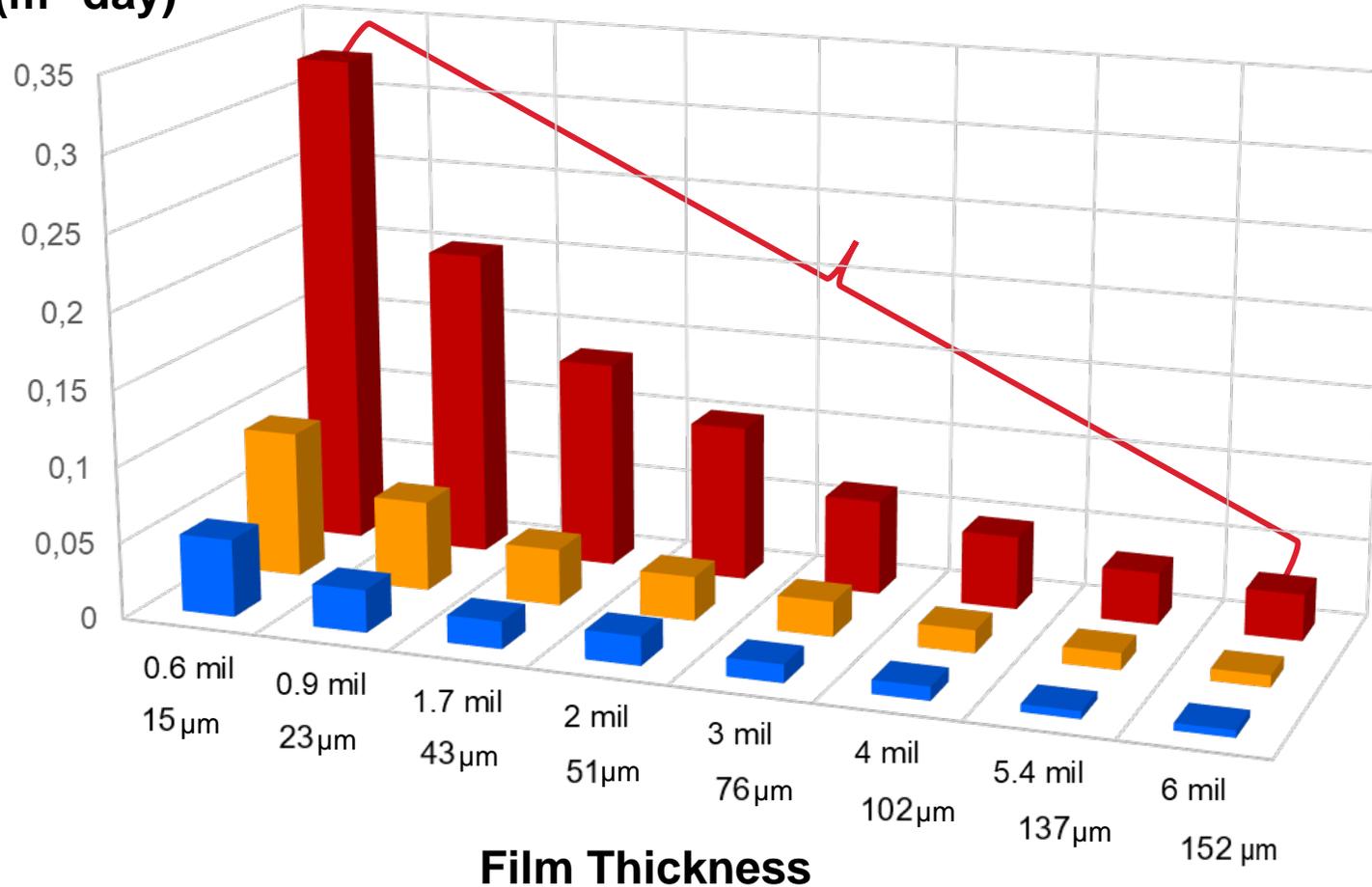
40°C / 75% RH "Accelerated"
30°C / 65% RH CZ IVa
25°C / 60% RH CZ II

Source:
Honeywell Aclar Datasheets

MVTR of Aclar depends on film thickness, temperature and humidity

Aclar MVTR (Flat-Film) @ Accelerated & ICH Testing Conditions

g/(m²*day)

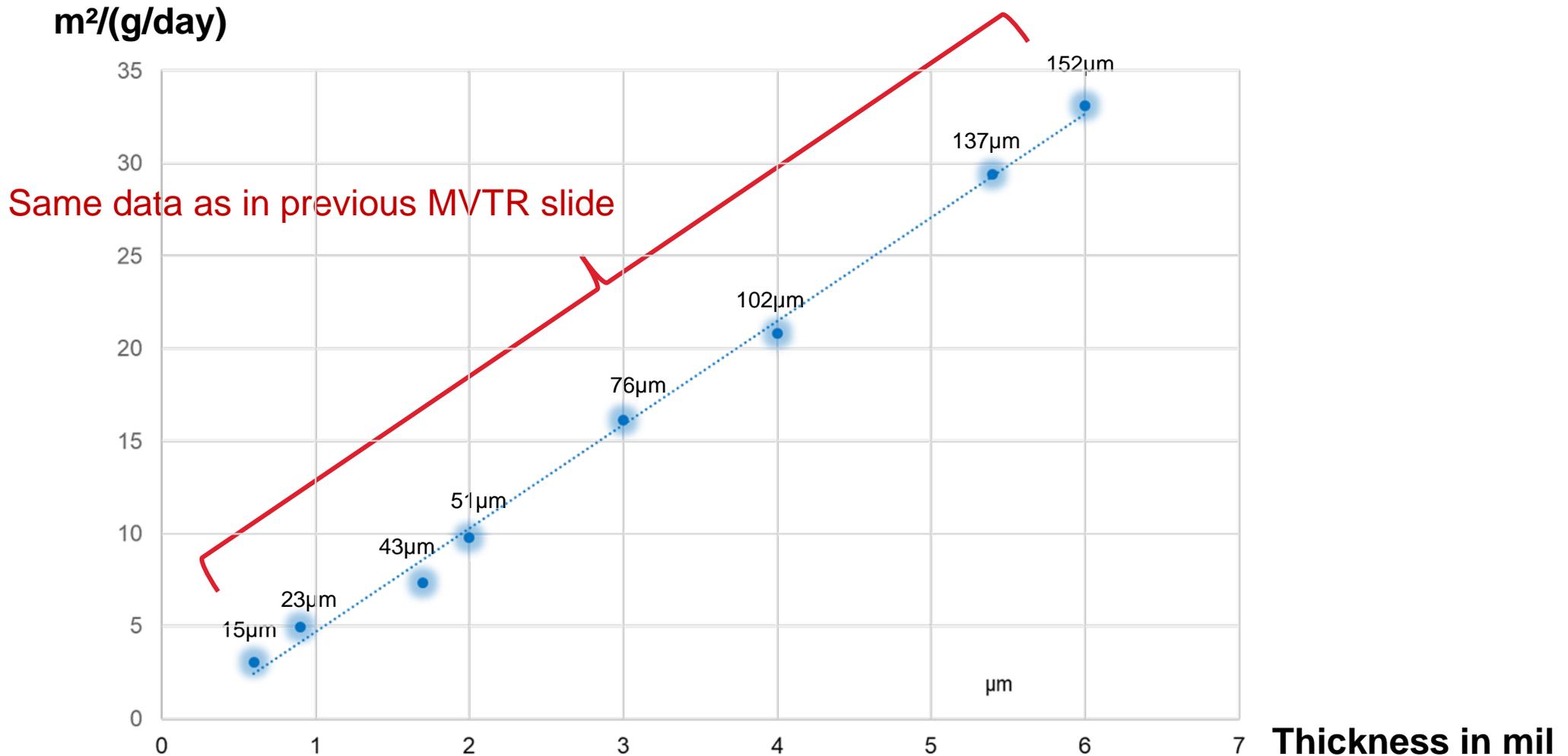


40°C / 75% RH "Accelerated"
30°C / 65% RH CZ IVa
25°C / 60% RH CZ II

Source:
Honeywell Aclar Datasheets

MVTR of Aclar depends on film thickness, temperature and humidity

Flat Film Barrier (1/MVTR) @ 40°C / 75% RH



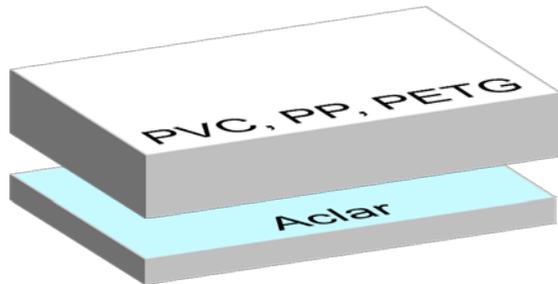
Source:
Honeywell Aclar Datasheets

Barrier of Aclar proportional to film thickness (T & RH constant)

Common ACLAR®- Laminates

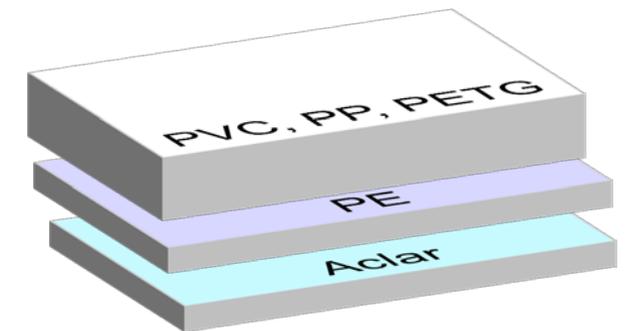
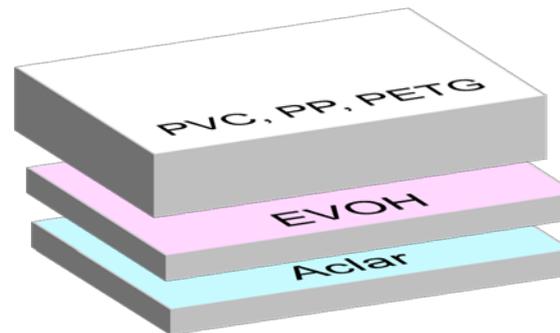
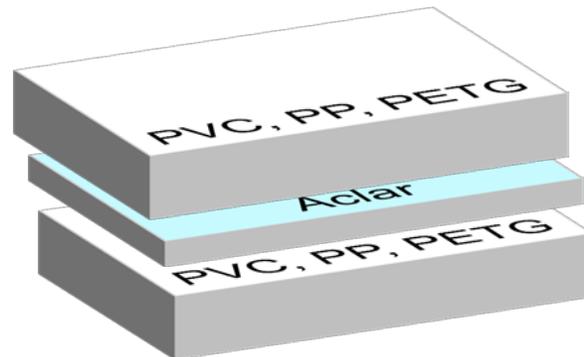
Duplex

- Asymmetrical structure
 - Aclar moisture barrier
 - Web carrier such PVC, PP, PETG



Triplex (and Quadruplex)

- Symmetrical structure
 - Aclar moisture barrier
 - Two outer layers such PVC, PP, PETG
- Asymmetrical structure
 - Aclar moisture barrier
 - Web carrier such PVC, PP, PETG
 - Oxygen barrier layer such EVOH
 - Other functional layers such as PE



Impact of forming

- Creation of greater surface S
- Reduction of film thickness d
- Inhomogeneous film thickness across surface

Options to assess MVTR (formed cavity)

1. Weight-gain testing
2. Calculations*

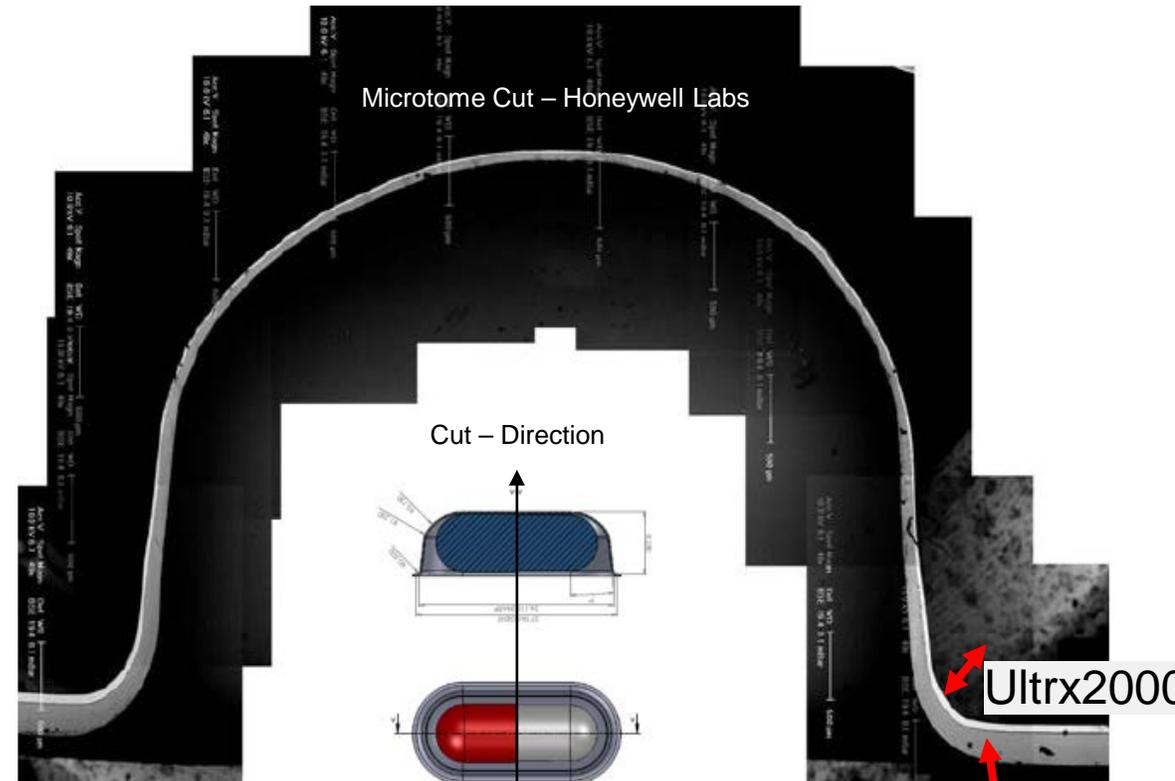
Formula to estimate per cavity MVTR:

$$MVTR (formed\ cavity) = S(base) * MVTR (flat\ film) * Draw\ Ratio^2$$

{mg/ cavity /day} {mm²} {mg/mm²/day}

$$Draw\ Ratio = \frac{S(formed\ cavity)}{S(base)}$$

* Assumption: Homogenous thickness-distribution, inversely proportional to surface



Size 1 capsule:

$S(base) = 193.2\text{ mm}^2$

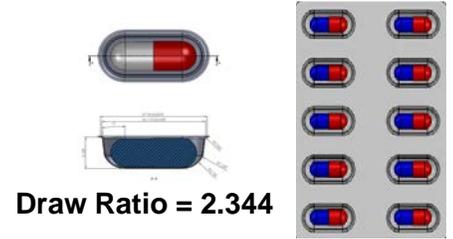
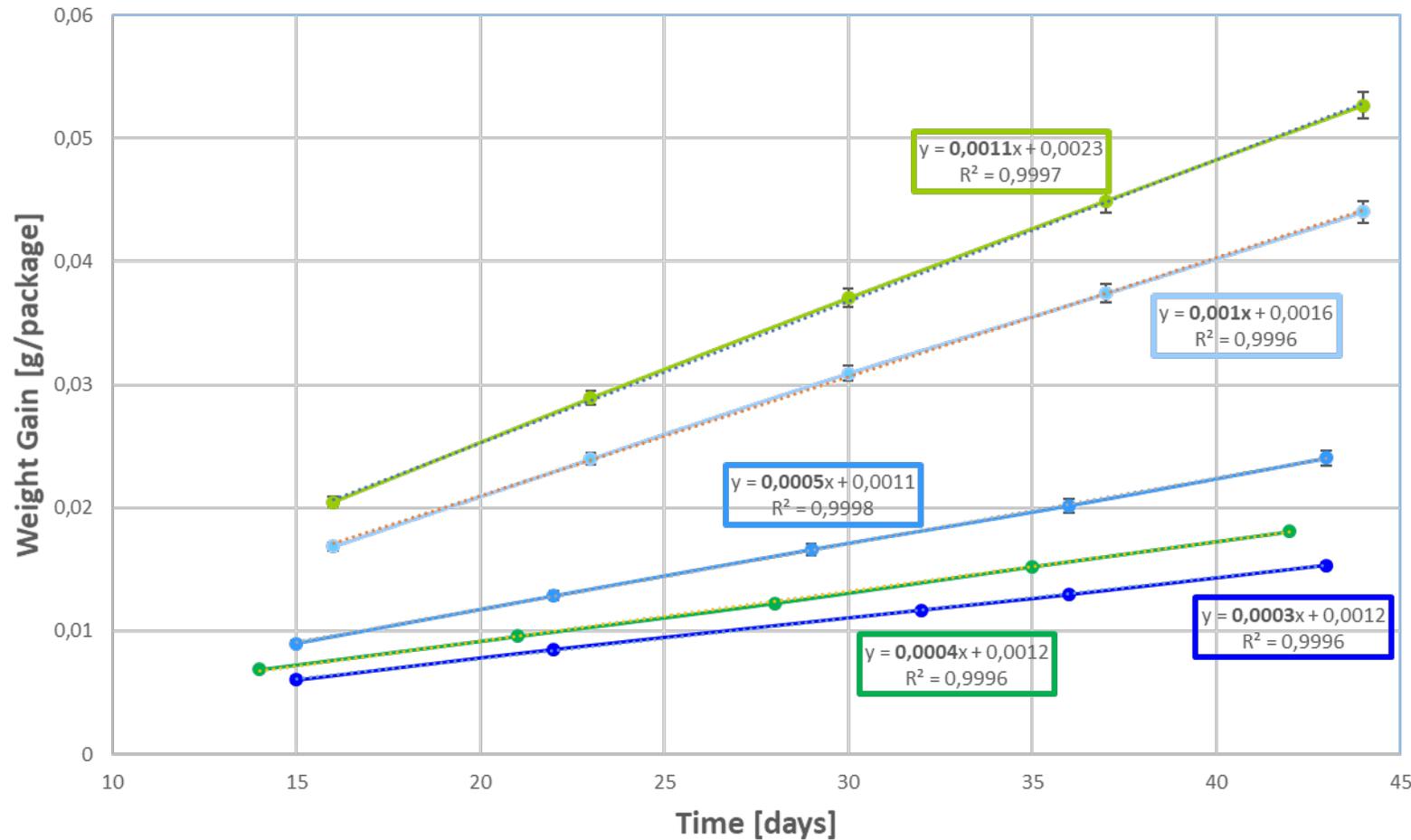
$S(formed\ cavity) = 452.8\text{ mm}^2$

→ $Draw\ Ratio = 2.344$

Formed cavity MVTR critical for drug product stability

Weight-Gain Testing – Size #1 Capsule

Size#1 capsule run with plug-assist **40°C / 75% RH**

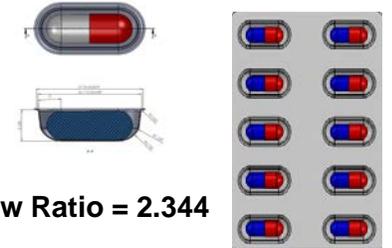


- Aclar Accel 1700
- Aclar UltRx2000
- Aclar UltRx4000
- Aclar Accel 5400
- Aclar UltRx6000

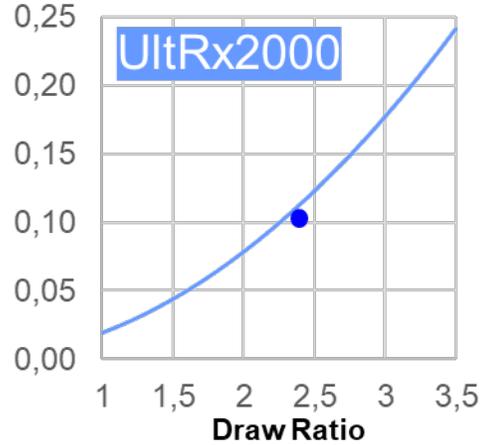
Example of weight gain testing according to USP 671

Per Cavity MVTR - Measured vs Calculated

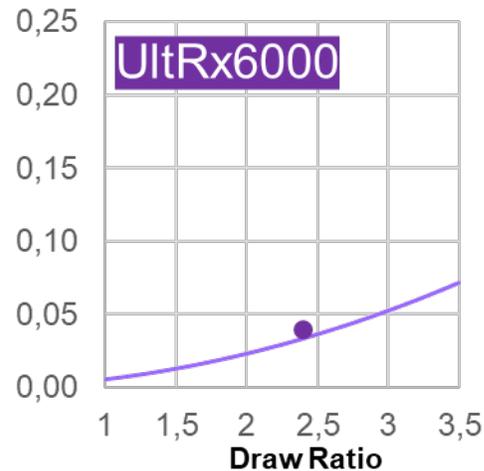
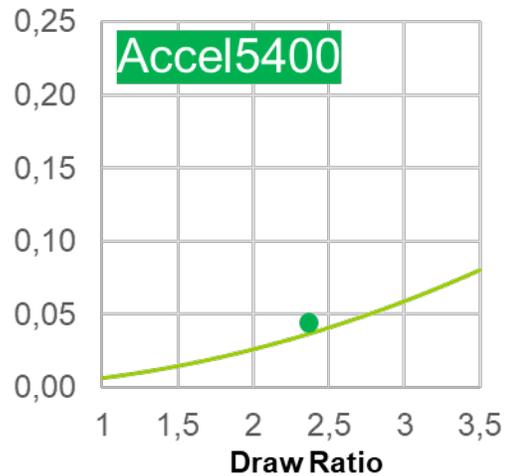
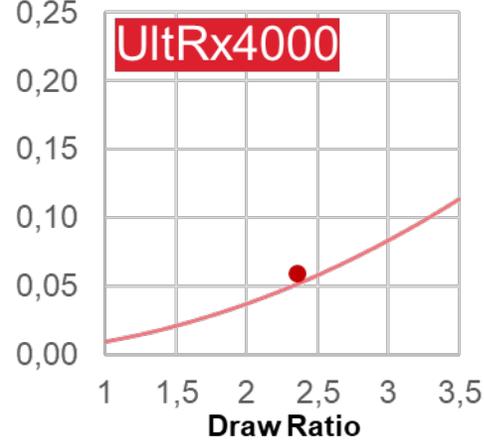
Size#1 capsule run with plug-assist **40°C / 75% RH**



mg/cavity/day

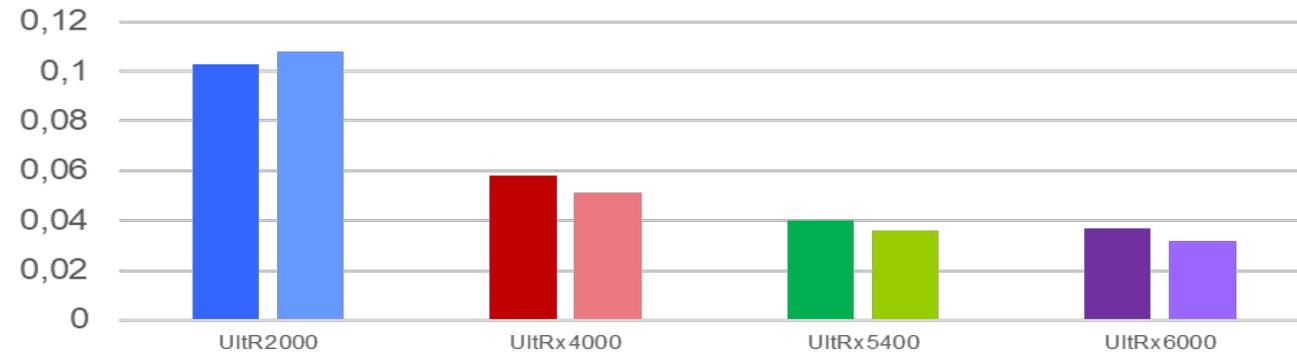


mg/cavity/day



Comparison MVTR (mg/cavity*day)							
UltRx2000		UltRx4000		Accel5400		UltRx6000	
Weight gain	Barrier Calcs	Weight Gain	Barrier Calcs	Weight Gain	Barrier Calcs	Weight Gain	Barrier Calcs
0,103	0,108	0,058	0,051	0,04	0,036	0,037	0,032

mg/cavity/day



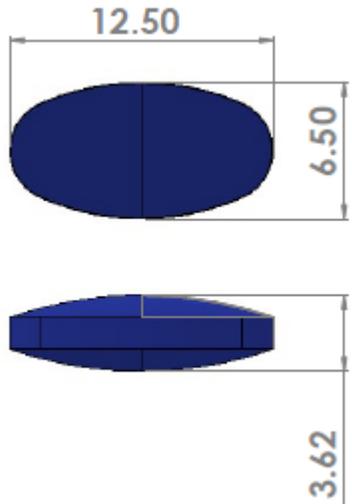
Left bar: Measured Right bar: Calculated

Deviations measured vs calculated are in the range of -5% - +13.5%

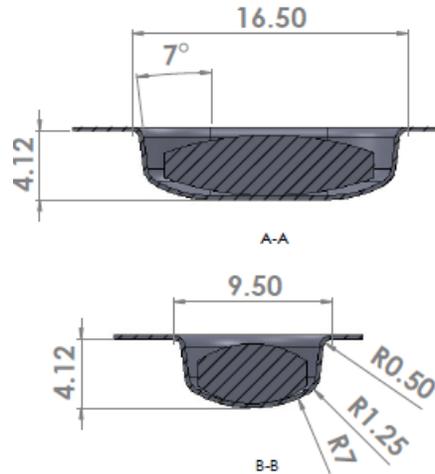
Decent correlation of weight gain testing results with calculations

Honeywell Services Example

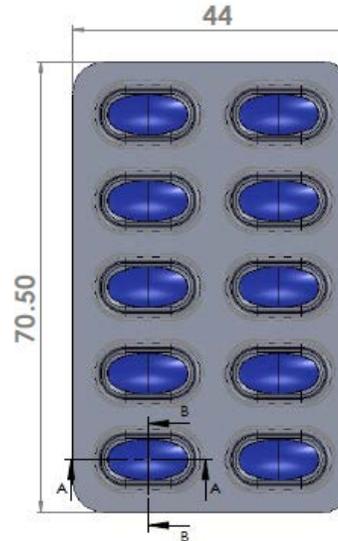
1. Tablet geometry



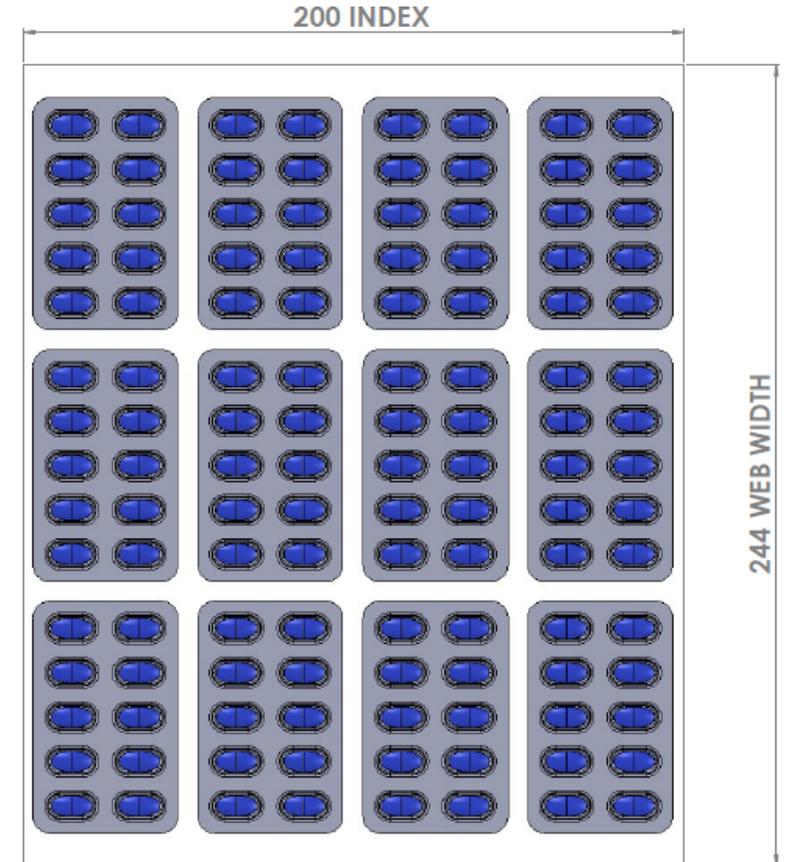
2a. Cavity geometry
2b. Per Cavity MVTR



3. Blister Lay-out



4. Web-Lay-out



Per cavity MVTR prediction for selected Aclar grades

Aclar Ultrx2000			Aclar Ultrx4000			Aclar ACCEL5400			Aclar Ultrx6000		
25°C/60 %RH	30°C/65 %RH	40°C/75% RH	25°C/60% RH	30°C/65 %RH	40°C/75% RH	25°C/60% RH	30°C/65 %RH	40°C/75 %RH	25°C/60% RH	30°C/65% RH	40°C/75% RH
0.009	0.016	0.047	0.004	0.008	0.023	0.003	0.006	0.017	0.003	0.005	0.016
+/-0.003	+/-0.003	+/-0.005	+/-0.001	+/-0.001	+/-0.003	+/-0.001	+/-0.001	+/-0.002	+/-0.001	+/-0.001	+/-0.002

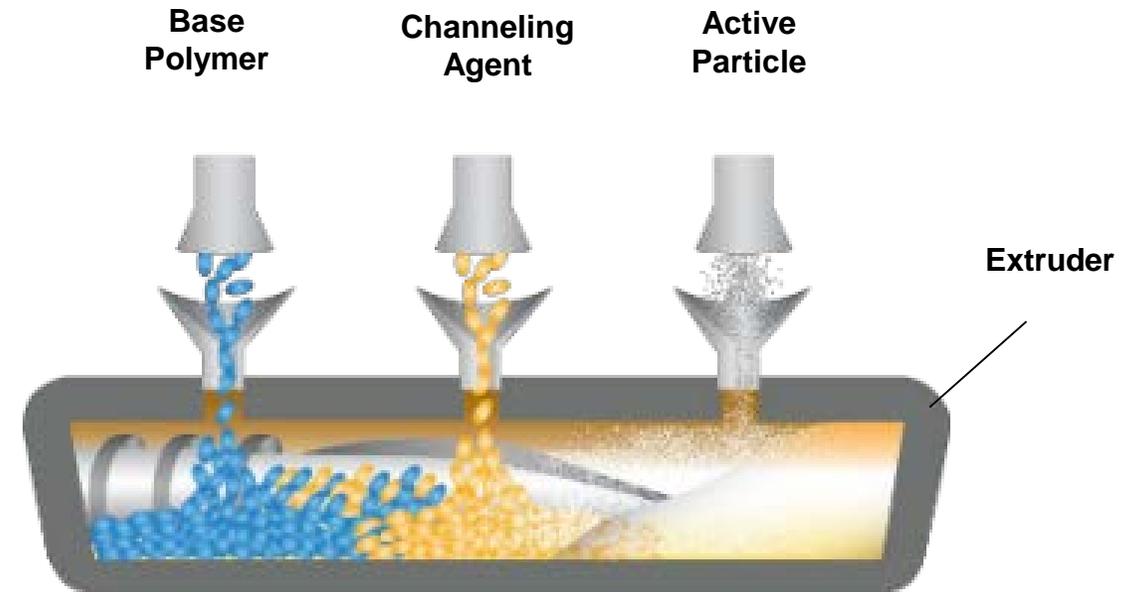
From tablet geometry to cavity design, blister card design to final web-lay-out

3-Phase Activ-Polymer™ Material

Material Science: Adding Chemistry to Polymers

3-Phase Polymers

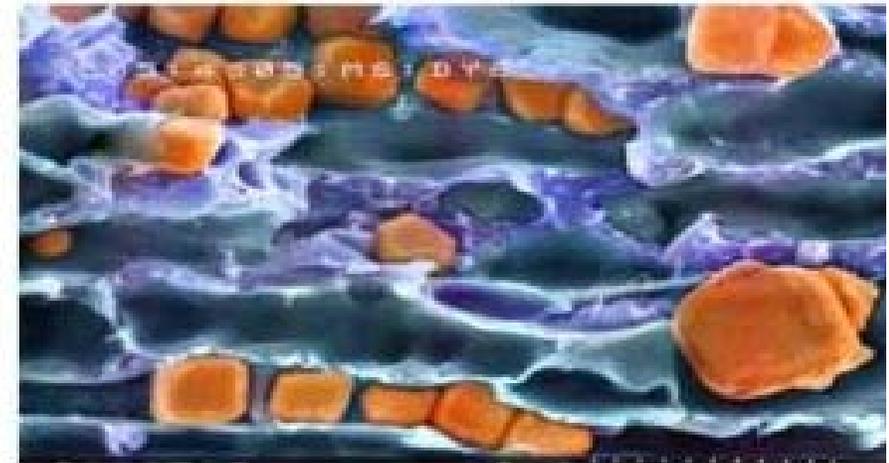
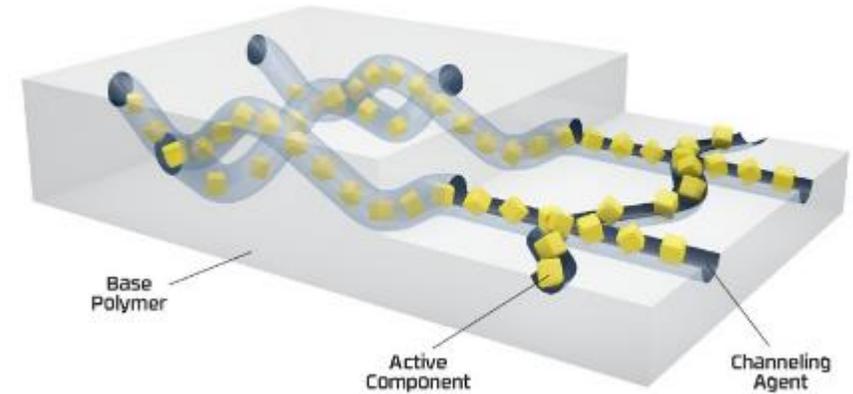
1. Majority Polymer: Base structure component
2. Minority Polymer/Channeling Agent: Immiscible in majority polymer
3. Particle: Adsorbing/adsorbing – active component



3-Phase Activ-Polymer™ Applications

- Channels created within a polymer allow movement of gases
 - **Moisture Control**
 - **Scavenge:** odors, formaldehyde, and VOCs
 - **Release/Emitting:** aromas, biocides, nutrients, carbon dioxide
 - **Antimicrobial:** pathogen reduction
- **Gas diffusion** is controlled through the channel composition

CSP Activ-Polymer™ Technology

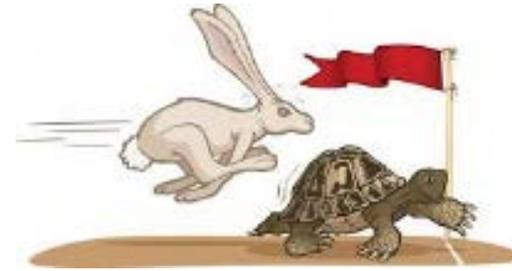


Active Packaging – Putting Chemistry into Polymers

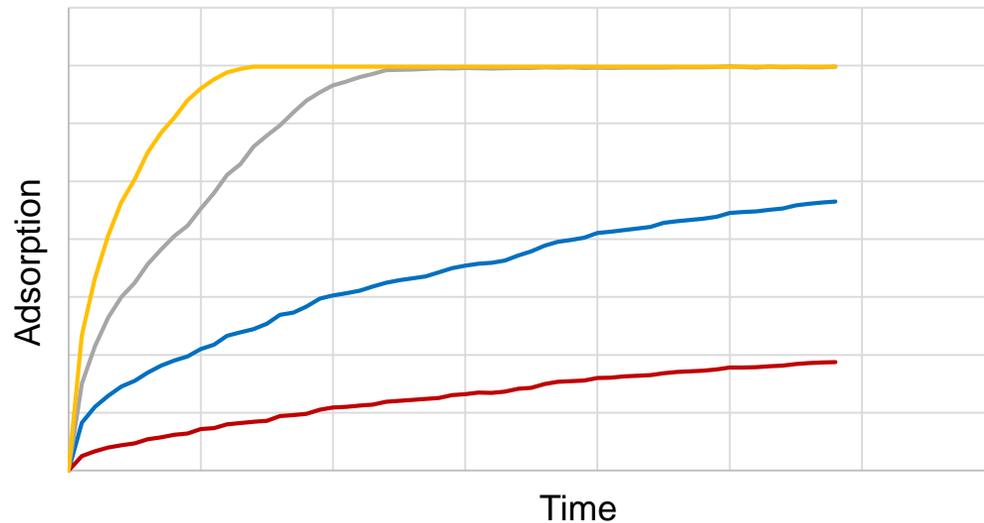
3-Phase Activ-Polymer™ Material

3-Phase Activ-Polymer™ material allows the **control of kinetics** based upon formulation

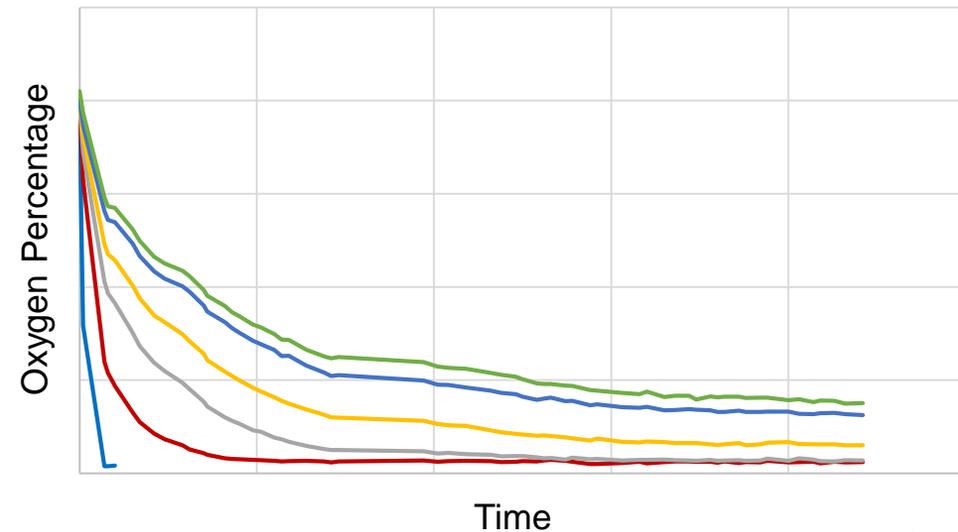
- Uptake rate can be increased or decreased
- Capacity can be increased or decreased



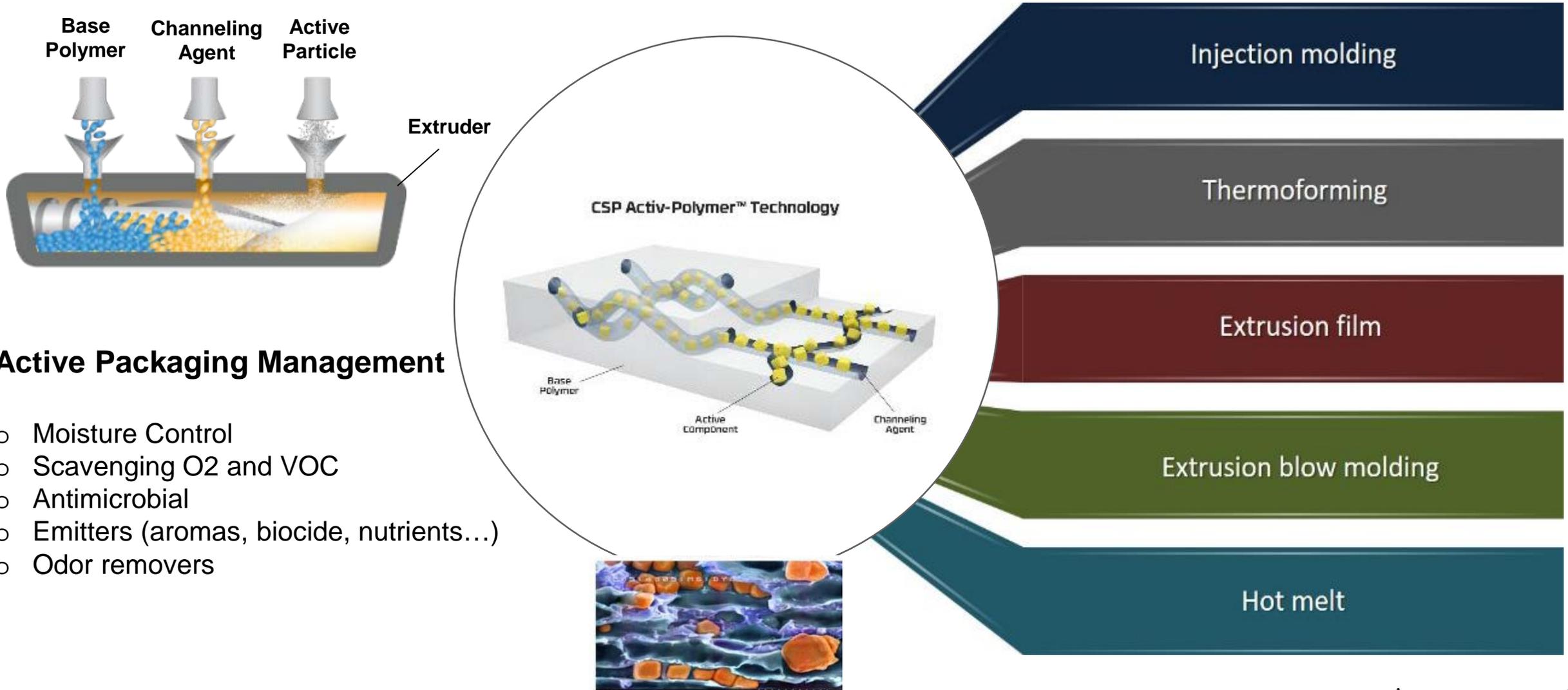
Moisture Adsorption Kinetics



Oxygen “Pull-Down” Performance



3-Phase Activ-Polymer™ Material = Platform Material



Active Packaging Management

- Moisture Control
- Scavenging O2 and VOC
- Antimicrobial
- Emitters (aromas, biocide, nutrients...)
- Odor removers

Protecting OSD from Moisture

Existing packaging options for Pharma

2nd packaging sachet



- Adds materials and size to packaging
- Complexity for end-user
- Desiccant protection ends when outer pouch is opened

Fishbone design



- Adds materials and size to packaging
- Complexity for end-user
- Ambient moisture exposure of any OSD that shares a desiccant when common barrier is breached

Cold form foil



- Good barrier protection
- Fails to address initial residual moisture
- Increased blister card size vs thermoform
- Capsule is not visible # compliance

Activ-Blister™ Solutions = Protection with Flexibility

- Management of all sources of moisture
 - Initial OSD moisture, residual moisture in the headspace and moisture transmitted during blister storage
 - Combination options available (e.g. moisture + oxygen)
- Customized capacity and uptake rates
- Integrated with a Film Applicator Module (heatstaking) into existing and new packaging lines



Case Study: FreeThink and PCI

Superior Protection of a Model Drug Product Over Cold-Form

- Compared efficacy of Activ-Blister™ packaging configurations using Aclar grade barrier film with cold-form foil in maintaining the stability of a model tableted drug product.
- An Accelerated Stability Assessment Program (ASAP) study was carried out and growth of the main degradant of the active ingredient was quantified.
- Data were modeled using the *ASAPprime*® software and included four different packaging configurations:
 - Cold-form foil blisters
 - Aclar® UltRx4000 thermoform incorporating Activ-Blister™ technology with molecular sieve,
 - Aclar® UltRx4000 thermoform incorporating Activ-Blister™ technology with silica gel
 - Aclar® UltRx4000 Thermoform blisters alone.
- Two initial relative humidities (30% and 60%) were modeled to assess the impact of starting water content on shelf-life.

Case Study

Objective: Compare efficacy of Activ-Blister™ packaging configurations with cold-form foil in maintaining the stability of a model tableted drug product.

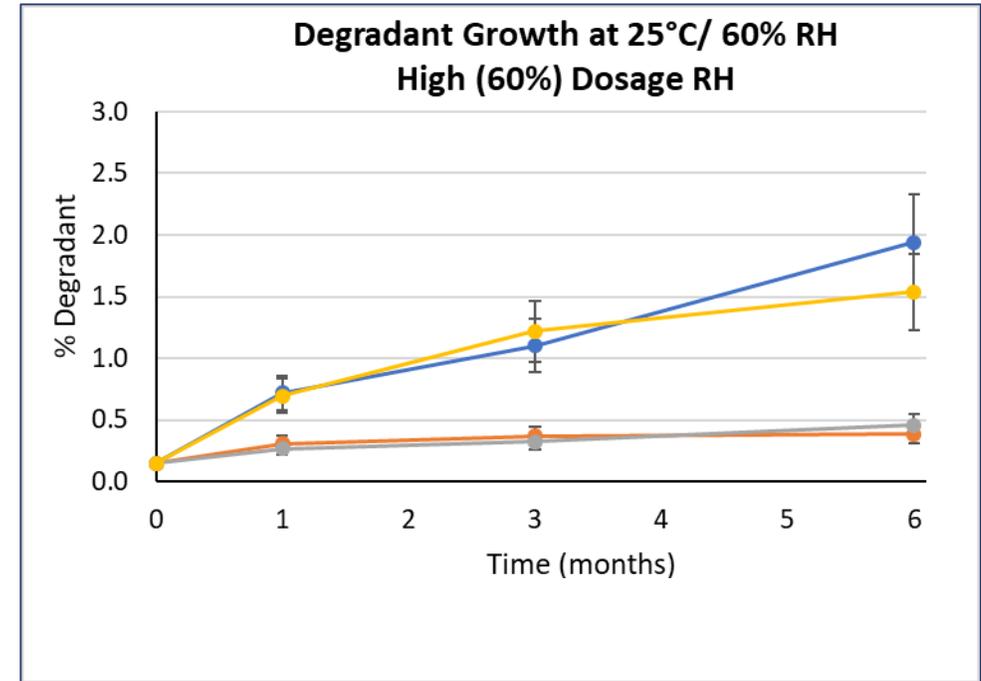
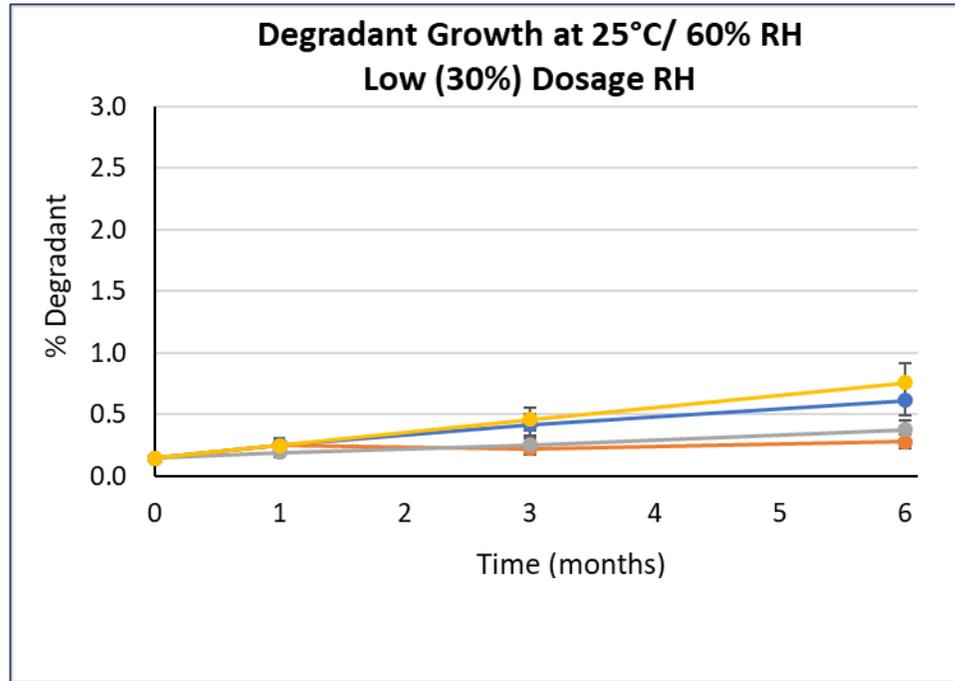
Blistering & Storage Conditions for Stability Study:

Packaging Configuration	Low Water Content, 25°C/60% RH	Low Water Content, 30°C/65% RH	Low Water Content, 30°C/75% RH	High Water Content, 25°C, 60%RH
	1, 3, 6 months			
Aclar® Thermoform Activ-Film™ Molecular Sieve (Activ-Blister™)	X	X	X	X
Aclar® Thermoform Activ-Film™ Silica Gel (Activ-Blister™)	X	X	X	X
Cold-form foil	X	X	X	X
Aclar® Thermoform without Activ-Film™	X	X	X	X

ICH storage conditions evaluated: 25°C/60% RH, 30°C/65% RH and 30°C/75% RH.

Case Study - Data

Growth of main degradant in tablets stored under ICH stability conditions under different packaging configurations with Low residual humidity (30%) vs High residual humidity (60%)

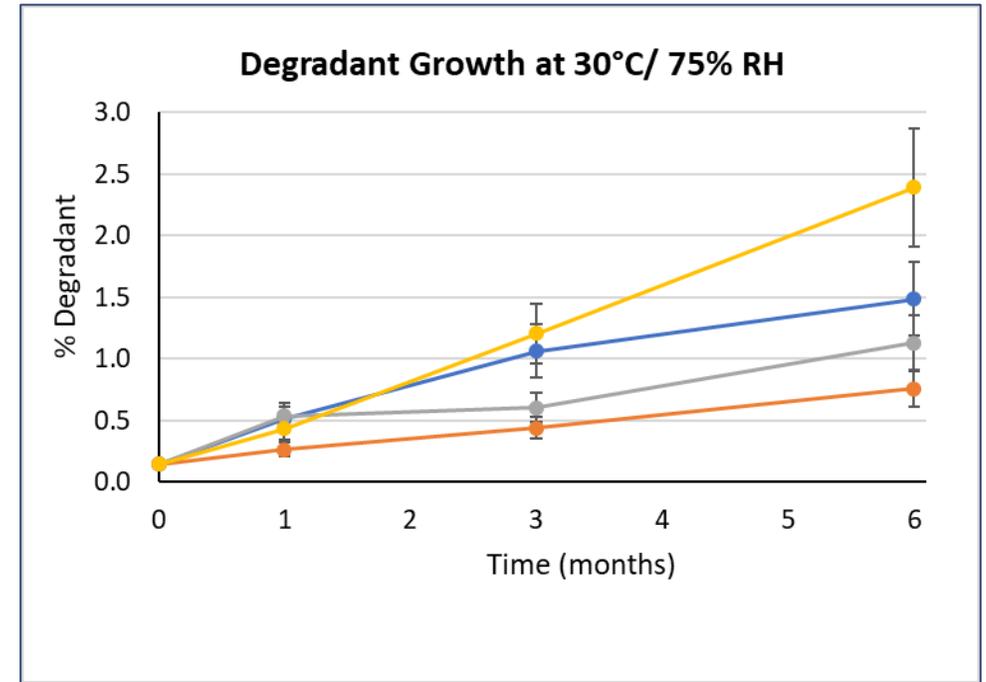
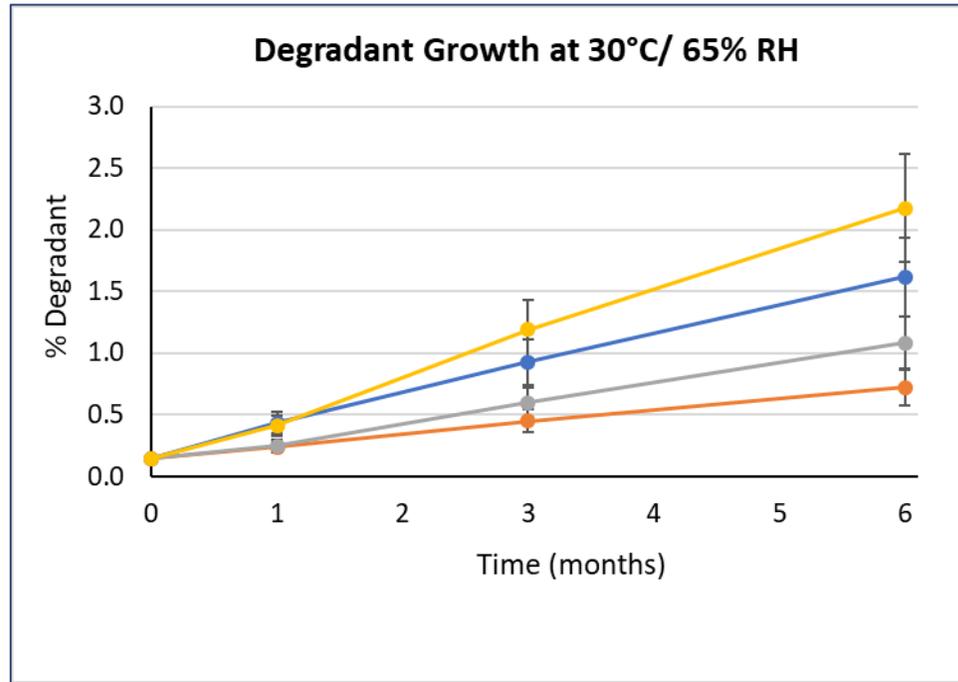


- **Aclar® UltRx4000 Thermoform Blister**
- **Cold-Form (alu/alu) Blister**
- **Activ-Blister™ with Silica Gel and Aclar® UltRx4000 Thermoform film**
- **Activ-Blister™ with Molecular Sieve and Aclar® UltRx4000 Thermoform film**

Data courtesy of joint study with FreeThink Technologies

Case Study - Data

Growth of main degradant in tablets stored under ICH 4 stability conditions



- **Aclar® UltRx4000 Thermoform Blister**
- **Cold-Form (alu/alu) Blister**
- **Activ-Blister™ with Silica Gel and Aclar® UltRx4000 Thermoform film**
- **Activ-Blister™ with Molecular Sieve and Aclar® UltRx4000 Thermoform film**

Data courtesy of joint study with FreeThink Technologies

Case Study – Conclusions

The packaging configurations for moisture sensitive API can be ranked in the following way:

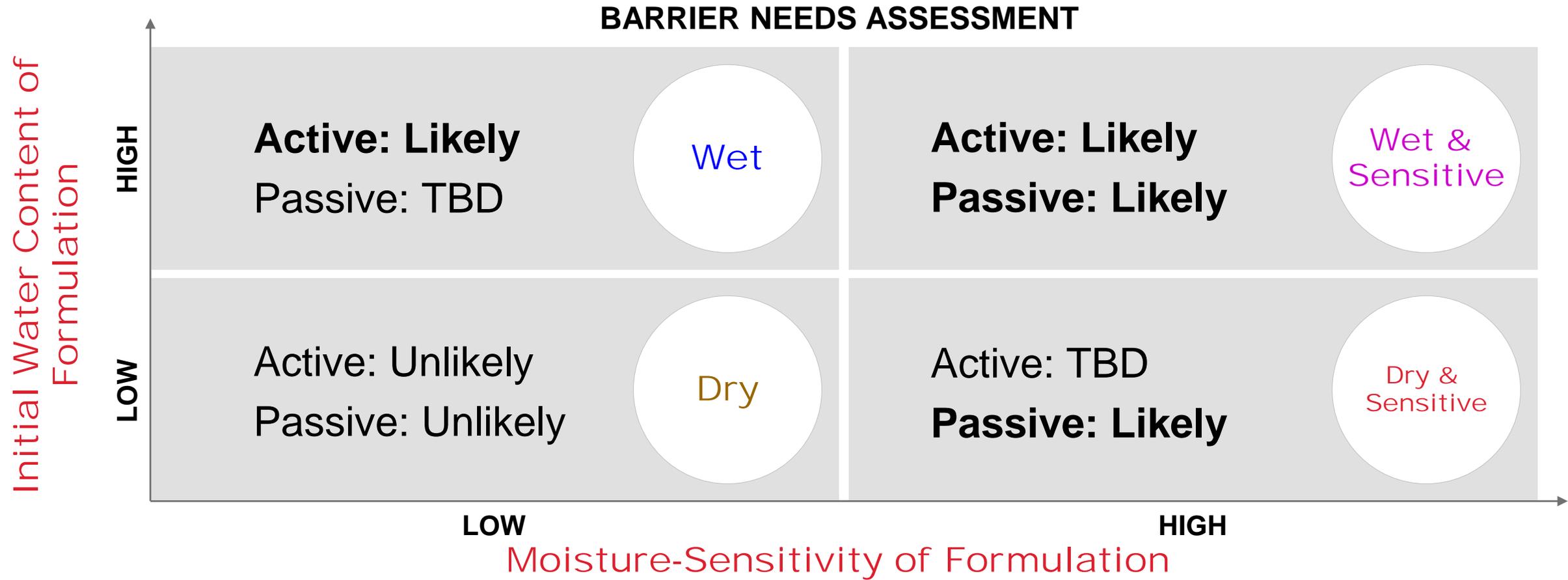


Least protective to degradation

Most protective to degradation

- The advantage of Aclar® thermoform combined with Activ-Blister™ Solutions over cold-form foil is particularly pronounced for drug product with a high initial water content.
- Activ-Blister™ packaging combines the practical advantages of thermoform blisters with the moisture protection provided by desiccant for enabling a thermoform option for highly moisture-sensitive drug products.

Active Packaging & Passive Barrier Needs

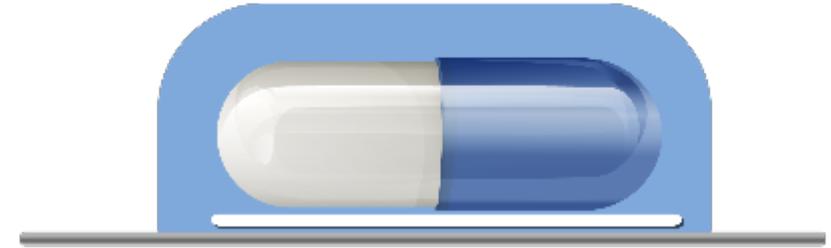


Four main categories to be assessed in more detail

Aclar® and Activ-Blister™ Solutions

Value for Oral Solid Dose Packaging

1. Move from bottle to blister
 - Discrete headspace management in each blister
2. Avoid lengthy development and reformulation for ICH 3&4
3. Reduce packaging complexity and costs
 - Eliminate purging / secondary and fishbone packaging
4. Move from coldform to thermoform
 - Visible capsule / tablet – Increase compliance
 - Smaller footprint (40-60% size reduction)
5. Enhance shelf life when needed



Questions for our speakers?



Kori Anderson

General Manager, Life Science Packaging
Honeywell International



François Bidet

VP Business Development, EMEA
Aptar CSP Technologies



Dr. Thomas Dries

Global Market Development Manager
Honeywell International



Jim Hollinger

Activ-Film™ Business Unit Manager
Aptar CSP Technologies

References

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Sandeep Kalepua; Vijaykumar Nekkantib Acta Pharmaceutica Sinica B; Vol. 5, Issue 5, Sep 2015, pp 442-453
<https://doi.org/10.1016/j.apsb.2015.07.003>
- 2: Stabilization of amorphous drugs; are crystalline inorganic excipients a way forward?
Eric Ofosu Kissi and Thomas Rades
PSSRC Pharmaceutical Solid State Research Cluster, Aug 24 2020
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